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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,56,59,60 and 62-65* is/are pending in the application.

4a) Of the above claim(s) *40 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,41-47,51,52,56,59,60,62,63 and 65* is/are rejected.

7)☒ Claim(s) *56,60,62 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed April 17, 2008. This action is made non final.

Claims 31, 35-38, 40-47, 51-52, 56, 59-60, and 62-65 are currently pending. Claims 31, 40-41, and 56 have been amended. Claims 62-65 are newly presented.

Further it was noted in the previous office action that Claim 40 was withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 23, 2006. It is noted that the rejection of claim 40 on the Office Action Summary Sheets from June 21, 2006 and February 22, 2007 is a typographical error. This claim has never been examined for patentability. The examiner regrets the confusion.

Newly submitted claim 64 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, claim 64 is drawn to a method of administering to a human patient an effective amount of an ErbB1 inhibitor, whereas the previously pending claims are drawn to a method of predicting the likelihood that a human colon cancer patient with respond to treatment

with an ErbB1 inhibitor, and thus they have different modes of operation and effects, since the conclusion drawn for each method versus the other is different. Further the previously pending claims require a step of nucleic acid analysis whereas claim 64 does not require such a step. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 64 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Declaration

2. The declaration under 37 CFR 1.132 filed April 14, 2008 is insufficient to overcome the rejection of claims 31, 35-38, 41-47, 51-52, 56, and 59-60 based upon enablement for the reasons presented below in paragraph 8.

Withdrawn Objections

3. The objection made to claim 57 in section 3 of the Office Action of October 19, 2007 is moot in view of the cancellation of claim 57.

Withdrawn Rejections

4. The rejection made under 35 USC 112 1st paragraph (new matter) in section 5 of the Office Action of October 19, 2007 is withdrawn in view of Applicants arguments which state that ErbB1 is synonymous with EGFR. Further the Applicants have cited references which demonstrate that even before the November 2002 priority date of the instant Application EGFR and ErbB1 were known to be synonyms.

Several of the rejections made under 35 USC 112 2nd paragraph in section 7 of the Office Action of October 19, 2007 are withdrawn in view of Applicants amendments. Any rejection not reiterated herein is considered withdrawn.

Claim Objections

5. Claim 56 is objected to because the claim, line 4 has a typo. Specifically the claim recites "to as to".

Claim 60 is objected to because the claim recites RNA transcripts which have not been elected.

Claim 62 is objected to because the claim recites determining the normalized level of Kirt17. However the gene is actually called KRT17.

Claim 63 is objected to because the claim, line 3 has a typo. Specifically the claim recites "assaying A normalized level".

Claim Rejections - 35 USC § 112 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 35-38, 41-47, 51-52, 56, 59-60, 62-63, and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 35-38, 41-47, 51-52, 59-60, and 62-63, are indefinite because the claims do not clearly set forth a step of predicting the likelihood that a human cancer patient will respond to treatment with an ErbB1 inhibitor. The claims do not recite a clear nexus between the preamble and the last step of the method because analyzing the normalized level of the LAMC2 transcript is not equivalent to predicting the likelihood that a human cancer patient will respond to treatment with an ErbB1 inhibitor. Further the "wherein" clause that states that the normalized level of LAMC2 RNA transcript correlates with patient response to treatment with an ErbB1 inhibitor is indefinite because "correlates" is not equivalent to "predicting".

Claims 56 and 65 are indefinite because the claims do not clearly set forth a step of using the expression level of LAMC2 to predict the likelihood that a patient diagnosed with an ErbB1 expressing colon cancer will respond to treatment with an ErbB1 inhibitor. The claims do not recite a clear nexus between the preamble and the last step of the method because analyzing the normalized level of the LAMC2 transcript is not equivalent to using the expression level of LAMC2 to predict the likelihood that a patient

diagnosed with an ErbB1 expressing colon cancer will respond to treatment with an ErbB1 inhibitor.

Response to Arguments

In the reply filed April 17, 2008 the Applicants amended the claims to recite a step of "analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor". The Applicants amendment has been considered but is insufficient to overcome the rejection. The Examiner suggests amending the claims to recite an actual step of "predicting". For example amending the claims to recite "predicting that the patient will have a decreased likelihood of response to treatment with an ErbB1 inhibitor if the normalized expression level of LAMC2 is elevated compared to a patient that does not have an elevated level of LAMC2".

Claim Rejections - 35 USC § 112 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 35-38, 41-47, 51-52, 56, 59-60, 62-63, and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claim 31 is drawn to a method for predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor. Claim 31 comprises (i) assaying a normalized level of LAMC2 in a sample comprising ErbB1 expressing cancer cells and (ii) analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor.

Claim 56 is drawn to a method of using the expression level of LAMC2 to predict the likelihood that a patient diagnosed with an ErbB1 expressing colon cancer will respond to treatment with an ErbB1 inhibitor. Claim 56 comprises (i) analyzing a normalized level of a LAMC2 transcript to predict a decreased likelihood of response if the normalized expression level of LAMC2 is elevated.

Claim 63 is drawn to a method for predicting the likelihood that a human cancer patient will respond to treatment with an ErbB1 inhibitor. Claim 63 comprises (i) assaying a normalized level of LAMC2 in a sample comprising ErbB1 expressing cancer

cells and (ii) analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor.

Claim 65 is drawn to a method of using the expression level of LAMC2 to predict the likelihood that a patient diagnosed with an ErbB1 expressing cancer will respond to treatment with an ErbB1 inhibitor. Claim 65 comprises (i) analyzing a normalized level of a LAMC2 transcript to predict a decreased likelihood of response if the normalized expression level of LAMC2 is elevated.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)). The nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor.

Scope of the Claims:

In the instant case the claims are extremely broad for several reasons. Claims 31 and 63 are broad because the claims are drawn to method for predicting the likelihood that a human cancer patient will respond to treatment with an ErbB1 inhibitor. The claims encompass a method wherein the inhibitor can be ANY inhibitor in the genus of ErbB1 inhibitors. Further the term "response" is broad in that it could encompass ANY type of response (i.e., remission of cancer, side effects, etc.). While claim 31 is limited to human patients with colon cancer, the human patients of claim 63 can have ANY type of cancer. The method comprises a first step of assaying the normalized level of LAMC2 in a sample comprising ErbB1 expressing cancer cells

obtained from the patient. Further the sample type is not limited to a specific type of cancer cell that expresses ErbB1. The method also comprises a second step of analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor, however the claim does not recite how one would use the LAMC2 level to make the prediction. Additionally the claims encompass a method of determining the level of ANY LAMC2 transcript.

Claims 56 and 65 are broad because the claims are drawn to method for using the expression level LAMC2 to predict the likelihood that a patient diagnosed with an ErbB1 expressing cancer will respond to treatment with an ErbB1 inhibitor. The claims encompass a method wherein the inhibitor can be ANY inhibitor in the genus of ErbB1 inhibitors. Further the term "response" is broad in that it could encompass ANY type of response (i.e., remission of cancer, side effects, etc.). While claim 56 is limited to patients diagnosed with ErbB1 expressing colon cancer, the patients of claim 65 can have ANY type of ErbB1 expressing cancer. Further the claims are not limited to human patients and therefore encompass other organisms such as cats, dogs, fish, etc. The method comprises analyzing the normalized level of the LAMC2 transcript so as to predict a decreased likelihood of response if the normalized level of LAMC2 is elevated. Here it is noted that the claims do not require a wet step and could therefore encompass a method of just looking at a patients chart to determine expression of LAMC2. Further the term "decreased likelihood of response" is broad because it is unclear what this is relative to. For example it is unclear if a person with an elevated LAMC2 level has a decreased likelihood of response in comparison to a person who

does not have a level LAMC2 level or some other person. Additionally the claims encompass a method of determining the level of ANY LAMC2 transcript.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several EGFR inhibitors are promising drug candidates for the treatment of EGFR expressing cancers. The specification further teaches the following EGFR inhibitors: (i) Iressa is a small synthetic quinazoline that competitively inhibits the ATP binding site of EGFR and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the EGFR and EGFR -dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas.

The specification (page 3) teaches that the present invention is based on findings of Phase II clinical studies of gene expression in tissue samples obtained from EGFR expressing head and neck cancer or colon cancer patients who responded well or did not respond to treatment with EGFR inhibitors.

The specification teaches (Example 2) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Following treatment with a single

unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Table 3 shows the results obtained using the partial response criterion. LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0357. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with EGFR inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to EGFR inhibitor (page 28). Table 4 shows the results analysis of colon cancer patient data using clinical benefit criteria. Here there is no data provided for LAMC2. Further with respect to claim 60 Table 4 shows that CD44v6 had a negative response and a p value of 0.0047.

The specification teaches (Example 1) 14 head and neck cancer patients were studied using a 192-gene assay. Following treatment with five unspecified EGFR inhibitors, four patients were determined to have had a partial response, two to have stable disease, and zero to have no complete response. Table 1 shows the results obtained using the partial response criterion. LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0017. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with EGFR inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to EGFR inhibitor (page 28). Table 2 shows the results analysis of head and neck cancer patient data using clinical benefit criteria. Again LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0342.

In the instant case the specification does not teach which ErbB1 inhibitors were used in examples 1 and 2. Therefore it is unclear if the claimed method can be used to predict the likelihood that a cancer patient will respond to treatment with any ErbB1 inhibitor. Further in example 1 all of the patients had ErbB1 expressing head and neck cancer and in example 2 all of the patients had ErbB1 expressing colon cancer. The specification does not teach an example wherein the patients had other types of cancer. Further all of the samples used in Examples 1 and 2 were either head and neck tumor tissues or colon tissues, yet the claims encompass a method wherein any sample can be used. Additionally the claims encompass a method wherein any LAMC2 transcript is measured. With respect to claims 56 and 65 the specification does not have an example in which other organisms were used as patients.

State of the Art and the Unpredictability of the Art:

The unpredictability of correlating a gene expression level with an individual's response to treatment is taught in the post filing date art by Evans (Nature 2004). Evans teaches that differences in DNA sequences that alter the expression or function of proteins that are targeted by drugs can contribute significantly to variation in the responses of individuals (Abstract). Evans teaches that most drug effects and treatment outcomes are determined by an interplay of multiple genes (Page 464 Column 2). Evans further teaches that although single gene defects can have a strong effect on their substrates, most of the phenotypic variability in drug response remains unexplained despite numerous efforts to interrogate candidate genes and pathways (Page 465, Column 1). Additionally Lee (The Oncologist 2005) teaches that while

genes likely contribute to the observed variability in cancer treatment outcome, there are several other variables that have been found to be associated with drug responses such as age, gender, diet, drug-drug interactions (Abstract).

In fact the unpredictability of correlating gene expression level to any phenotypic quality is taught in the art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of post genomics informatics, including gene networks, gene pathways, and gene ontologies (page 53). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). Additionally, post-filing art reveals that most gene association studies are hard to replicate. Lucentini (The Scientist) teaches that it is strikingly common for follow-up studies to find gene- disease associations wrong (page 2). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Lucentini teaches that bigger sample

sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (page 3).

Further the art of identifying if every ErbB1 inhibitor will be less effective in patients with increased LAMC2 levels is highly unpredictable. The genus of inhibitor drugs is expected to be very large. For example the post filing date art of Giaccone teach six EGFR inhibitors (Iressa, Tarceva, lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR inhibitor. For example Iressa and Tarceva inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. Thus it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that the LAMC2 gene is present in one organism (i.e. humans) does not allow one to conclude that this gene will present in other organisms and also be associated with the organisms response of EGFR inhibitors. The specification does not teach homologues of the LAMC2 gene in a representative number of different organisms. The specification also does not teach any other organisms which have EGFR expressing cancers. Thus it is unpredictable as to whether the LAMC2 gene, will also be over expressed in other organisms with EGFR

expressing cancer and if so if the over expression will be associated with decreased response to EGFR inhibitor drugs.

It is also unpredictable as to whether the results obtained with head and neck cancer patients and colon cancer patients can be extrapolated to patients with other types of EGFR expressing cancers. The teachings in the specification are limited to an association between the expression of LAMC2 and EGFR expressing head and neck cancer and colon cancer. There are no teachings in the specification regarding the expression of LAMC2 in other types of cancers that express EGFR. Accordingly, it is unpredictable as to whether the presently claimed method can be used to determine the likelihood that patients diagnosed with any type of cancer will respond to treatment with an EGFR inhibitor.

Quantity of Experimentation:

The specification asserts that patients diagnosed with ANY type of EGRF expressing cancer with elevated levels of LAMC2 are less likely to respond to a treatment with an EGFR inhibitor. However the specification only provides in examples in which patients diagnosed with head and neck cancer or colon cancer were used. Further the specification is silent as to which EGFR inhibitor was used therefore it is unclear if the claimed method would work for any EGFR inhibitor. Thus further experimentation would be required. For example, such experimentation may involve treating patients diagnosed with other types of EGFR expressing cancers with different types of EFGR inhibitors and conducting multiple gene expression assays to determine the expression levels of LAMC2. Further these patients would have to be monitored to

determine disease progression. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

The claims are drawn to a method for predicting the likelihood that patients diangosed with ErbB1 expressing cancer will respond to treatment with any ErbB1 inhibitor by determining the normalized level of LAMC2. As discussed above, whether an association exists between increased levels of LAMC2 and the response to ErbB1 inhibitors is highly unpredictably. In the instant case the specification has not taught a reliable method of associating increased levels of LAMC2 and the response to ErbB1 inhibitors. Accordingly, although the level of skill in the art of molecular biology is high,

given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Amendment

8. In the reply filed April 17, 2008 the Applicants traversed the enablement rejection. In response to the Arguments it is noted that the Applicants arguments are persuasive to the extent that the address the fact that ErbB1 is synonymous with EGFR. The Applicants continue to argue that they have shown that the over expression of LAMC2 in colon tumor tissue showed a negative (e.g., inverse) correlation with response to treatment with any of the EGFR inhibitors. The Applicants further state that they have shown a negative correlation between LAMC2 transcript levels and patient response to at least three classes of EGFR inhibitors. The Applicants have also submitted a declaration by Joffre B. Baker, Ph.D., one of the inventors, wherein Dr. Baker states that the patients were treated with an EGFR inhibitor selected from the group erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Both the Applicants arguments and Dr. Baker's declaration have been fully considered are not persuassive. In the instant case specification does not teach a method which uses the inhibitors disclosed in the declaration. Furthermore the specification does not even mention all of these inhibitors. Additionally it is pointed out that there is no specific data provided in the declaration for each drug that was tested or even each class of drug that was tested.

Therefore it is impossible for one to conclude that over expression of LAMC2 will be negatively correlated with response to treatment with any EGFR inhbitor. Furthermore, the Applicants do not teach the molecular mechanisms or biochemical characteristics of LAMC2 that would lead one of ordinary skill in the art to understand its role and/or levels of expression required for LAMC2 transcripts, such that said expression level would be predictive of a given clinical outcome. Thus one cannot readily anticipate the effect of the level of LAMC2 on the response to treatment with ANY ErbB1 inhbitor.

Next the Applicants argue that the term "response" refers to a response in terms of the cancer itself. This argument has been fully considered but is not persuasive. In the instant case the term "response" is broad in that it could encompass any type of response and is not limited to a response in terms of the cancer itself. Further the specification does not define response in terms of cancer.

Additionally the Applicants argue that not every species in a genus has to be tested in order for a genus to be enabled. While this may be true Applicants are required to teach that a representative number of species in the genus are enabled. In the instant case this has not been done. While the declaration states that the Applicants have tested 5 different ErbB1 inhibitors there is no specific data provided in the declaration for each drug that was tested or even each class of drug that was tested. Further it is unknown which drug was used in Examples 1 and 2 of the instant specification.

The Applicants further argue that the teachings of Evans relate to a discussion of patient response to anti-hypertensive drugs and not EGFR inhibitors. This is true

however Evans was cited to generally teach that most drug effects and treatment outcomes are determined by interplay of genes and therefor is considered relevant. Lee was cited for teaching that while genes contribute to the observed variability in cancer treatment outcome there are other factors that are associated with drug responses. This is relevant because it shows how unpredictable the claimed method is because so many other factors besides the genetic factors contribute to a patient's drug response. Wu, Newton, and Lucentini were all cited because they teach in general how association studies based on gene expression are unpredictable. Based on reading these references one of skill in the art would doubt that there is actually a correlation between patient response to an ErbB1 inhibitor and LAMC2 transcript levels for several reasons i.e., because a small population was used, the assay has not been replicated etc. Cheung was cited for teaching how expression levels vary from person to person and therefore its unclear how much LAMC2 needs to be over expressed to be considered as indicative of decreased likelihood of response. Giaccone was cited for teaching how different EFGR inhibitors work by different mechanisms. This is important because it is unclear why the over expression of LAMC2 changes how one responds to a particular ErbB1 inhibitor.

Finally the Applicants argue that there would be no need to conduct "extensive experimentation". This argument has been fully considered but is not persuasive. For example the claims as amended now encompass a method wherein the patient has any type of ErbB1 expressing cancer, yet the specification only provides examples in which

the patients have head and neck cancer or colon cancer. For these reasons the enablement rejection is maintained.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31, 35-37, 56, 63, and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995).

Regarding Claims 31 and 63 Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal adenocarcinomas (Abstract). Hlubek does not specifically teach that the patients had ErbB1 expressing cancer cells, however Salomon teaches that collectively a total of 599 colon tumors have been examined in 12 separate studies and ~25-77% of the colon cancer patients have ErbB1 expressing cancer cells (Page 196, column 2), therefore in a population of 45 cases, ~11 to 35 of those cases would express ErbB1. Thus Hlubek teaches a method comprising (a) assaying the LAMC2 transcript in a sample comprising ErbB1 expressing cancer cells and (b) analyzing the level of the LAMC2 transcript. It is also noted that the claim recites "analyzing the level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor",

therefore since they prior art teaches analyzing the level of the LAMC2 transcript it must also teach predicting since the prior art teaches both of the claimed method steps of assaying and analyzing.

Regarding Claim 35 Hlubek teaches that the sample is a tissue sample (Page 8089, under heading "Tissue Specimens").

Regarding Claim 36 Hlubek teaches that the tissue samples were formalin fixed and paraffin embedded (Page 8089, under heading "Tissue Specimens").

Regarding Claim 37 Hlubek teaches that the tissue samples were from patients who underwent surgery. This is being interpreted as a biopsy (Page 8089, under heading "Tissue Specimens").

Regarding Claims 56 and 65 Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal adenocarcinomas (Abstract). Hlubek does not specifically teach that the patients had ErbB1 expressing cancer cells, however Salomon teaches that collectively a total of 599 colon tumors have been examined in 12 separate studies and ~25-77% of the colon cancer patients have ErbB1 expressing cancer cells (Page 196, column 2), therefore in a population of 45 cases, ~11 to 35 of those cases would express ErbB1. Thus Hlubek teaches a method comprising analyzing the level of the LAMC2 transcript. It is also noted that the claim recites "analyzing the level of the LAMC2 transcript so as to predict a decreased likelihood of response if the normalized expression level of LAMC2 gene is elevated in said patient", therefore since they prior art teaches analyzing the level of the

LAMC2 transcript it must also teach predicting since the prior art teaches the only require step of the claimed method (analyzing).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Comite (US 2002/0194022 filed 4/2002).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method further comprising preparing a report.

However Comite teaches a method of providing a patient with a report of the results from a medical consultation (para 0074).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by preparing a report comprising a statement where the patient is likely to respond to treatment with an ErbB1 inhibitor as suggested by Comite. This would be beneficial so that the patient and the patient's doctors could decide upon further treatment.

12. Claims 41-47, 52, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Bao (US 6251601 Issued 2001).

The teachings of Hlubek as evidenced by Salomon are presented above.

Hlubek does not teach a method wherein the expression of the LAMC2 transcript is determined using a microarray.

However Bao teaches that expression can be determined using an array of nucleic acid target elements attached to a solid support (abstract). Bao teaches that the nucleic acid target elements can be cDNAs (Column 6, lines 32-35). Bao teaches that the target elements can be between 100 bp and 5000 bp (column 8, lines 45-49). Bao

also teaches that the target elements can be oligomers ranging between 20 to 80 base pairs (Column 8, lines 27-30). Bao teaches that the array can contains about 100 to about 10,000 target sequences (Bao Column 9, lines 44-46). Bao teaches that any suitable substrate can be used including glass (Column 11, lines 37-40). Bao further teaches using a kit such as the QIAamp tissue kit for DNA extraction and isolation (column 12, l lines 13-16). Bao also teaches that the array can have nucleic acid analogs which are being interpreted as modified nucleic acids (column 7, lines 35-37).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by performing the expression analysis on a microarray as suggested by Bao. The microarray of Bao combines the capability of assessment of a large number of nucleic acids provided by microarray test formats to assess simultaneously both gene expression and genomic abnormalities in the same sample (Column 7, lines 9-22). Thus it would have been obvious to an ordinary artisan to use such an array to study colon cancer expression for the benefit of simultaneously determining gene expression and genomic abnormalities.

13. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Lehmann (Methods 2001).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method wherein RNA is isolated from cells present in a fixed paraffin embedded tissue by incubating the tissue section at a

temperature of about 56ºC to 70ºC in a lysis buffer in the presence of a protease without prior dewaxing, cooling the lysis solution and then isolating the RNA from the cooled lysis solution.

However Lehmann teaches a method of isolating RNA from paraffin embedded tissue wherein paraffin embedded tissue is digested without deparaffinization in lysis buffer with proteinase K overnight at 55º. The next day the samples are centrifuged at 4ºC which causes the paraffin to resolidify and the RNA is isolated form the cooled lysis solution (page 412 under "Isolation of RNA" and page 417 under "Protocol 3".

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lehmann particularly since Lehmann teaches that omission of deparaffinization and rehydration saves time, prevents the risk of RNA degradation during rehydration and reduces sample cross contamination from repeated pipetting. Further Lehmann teaches that the incubation time for extraction of the tissue specimens in a lot shorter (page 413).

14. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Chun (J Korean Med Sci 2000).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method wherein the expression of CD44v6 is also determined.

However Chun teaches that they determined the expression level of CD44v6 in colorectal tumors (Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by assaying the expression level of CD44v6 in colorectal tumors as suggested by Chun especially since Chun teaches that CD44v6 can be a molecular marker for colorectal cancer and its micro metastasis.

15. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Notterman (Cancer Research 4/2001) as evidenced by Affymetrix array finder (www.affymetrix.com).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method wherein the expression of Krt17 is also determined.

However Notterman teaches that they determined the expression level of multiple genes in samples obtained from patients with colorectal tumors. They further teach using the Affymetrix Human 6800 GeneChip (page 3124). As evidenced by Affymetrix this gene chip contains the Krt17 gene. Therefore Notterman teaches determining the expression level of the Krt17 gene.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by assaying the

expression level of Krt17 in colorectal tumors as suggested by Notterman for the benefit of determining which other genes are expressed differentially in colorectal cancer.

Response To Arguments

16. In the response filed April 17, 2008, the Applicants also traversed the art rejections. Regarding the rejection made over Hlubek the Applicants amended the claims and state that Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor. This argument has been fully considered but is not persuasive because the claims do not actually require an active process step of "predicting". Amending the claims to recite an active process step of "predicting" would overcome this rejection.

Regarding the rejections made over Hlubek in view of Bao and over Hlubek in view of Chun the Applicants argue that Bao and Chun do not cure the deficiencies of Hlubek. However for the reasons recited above Hlubek teaches all of the required method steps. Therefore all of the art rejections have been maintained.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner
Art Unit 1634

/Carla Myers/
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